exploring the biology of human adipocyte progenitor cells in their microenvironment and for testing whether findings obtained with a rodent model are relevant to human physiological or patho-physiological conditions.

REFERENCES

Abdou, H.S., Atlas, E., and Haché, R.J. (2013). Endocrinology *154*, 1454–1464.

Arner, P., Andersson, D.P., Thörne, A., Wirén, M., Hoffstedt, J., Näslund, E., Thorell, A., and Rydén, M. (2013). J. Clin. Endocrinol. Metab. *98*, E897–E901.

Laplante, M., Horvat, S., Festuccia, W.T., Birsoy, K., Prevorsek, Z., Efeyan, A., and Sabatini, D.M. (2012). Cell Metab. *16*, 202–212.

Lee, M.J., Fried, S.K., Mundt, S.S., Wang, Y., Sullivan, S., Stefanni, A., Daugherty, B.L., and Hermanowski-Vosatka, A. (2008). Obesity (Silver Spring) *16*, 1178–1185.

Lindroos, J., Husa, J., Mitterer, G., Haschemi, A., Rauscher, S., Haas, R., Gröger, M., Loewe, R., Kohrgruber, N., Schrögendorfer, K.F., et al. (2013). Cell Metab. *18*, this issue, 62–74.

Tchkonia, T., Thomou, T., Zhu, Y., Karagiannides, I., Pothoulakis, C., Jensen, M.D., and Kirkland, J.L. (2013). Cell Metab. *17*, 644–656.

Veilleux, A., Côté, J.A., Blouin, K., Nadeau, M., Pelletier, M., Marceau, P., Laberge, P.Y., Luu-The, V., and Tchernof, A. (2012). Am. J. Physiol. Endocrinol. Metab. *302*, E941–E949.

Betatrophin Fuels β Cell Proliferation: First Step toward Regenerative Therapy?

Heiko Lickert[1,2,*]
[1]Institute of Diabetes and Regeneration Research
[2]Institute of Stem Cell Research
Helmholtz Center Munich, Am Parkring 11, 85748 Garching, Germany
*Correspondence: heiko.lickert@helmholtz-muenchen.de
http://dx.doi.org/10.1016/j.cmet.2013.06.006

Millions of diabetic patients are waiting for better treatment options, ideally by replenishing the lost or dysfunctional insulin-producing β cell mass. Yi et al. (2013) now identify Betatrophin, a hormone that specifically increases β cell proliferation with promising therapeutic potential.

Pancreatic β cells are perfect sensors of blood glucose levels and secrete just the right amount of insulin into the bloodstream to systemically regulate glucose and energy homeostasis. Type 1 diabetes results from autoimmune destruction of β cells, whereas in type 2 diabetes, a failure of β cells to compensate for peripheral insulin resistance leads to exhaustion, dedifferentiation, and loss of functional β cell mass. Unfortunately, neither pharmacological treatment nor insulin injections can fully substitute for endogenous β cell function to prevent uncontrolled hyperglycemia and the devastating micro- and macrovascular complications associated with both forms of diabetes. Thus, the only way for a better treatment and a potential cure for the disease is to replace or regenerate the lost or dysfunctional β cell mass (Bonner-Weir and Weir, 2005). Work by the Melton laboratory now reports on Betatrophin, a hormone that specifically increases β cell mass in mice and therefore raises hope for regenerative β cell therapy in humans (Yi et al., 2013).

It has long been known that insulin resistance causes compensatory β cell mass expansion in the pancreas, likely due to circulating growth factor(s) (Michael et al., 2000). Identification of these factors could possibly allow regenerative β cell therapy. Gut-derived incretins, macrophage-derived cytokines, muscle-derived myokines, and adipocyte-derived adipokines have all been shown to increase β cell mass but remain unchanged in the peripheral bloodstream of insulin-resistant mice (El Ouaamari et al., 2013). In a recent study published in *Cell* (Yi et al., 2013), a novel pharmacological mouse model of severe insulin resistance was used to identify these unknown factor(s) that trigger compensatory β cell proliferation. For this purpose, a 43 amino acid inhibitory peptide with high affinity and selectivity for the insulin receptor was infused into mice. Inhibition of insulin signaling caused dose-dependent hyperglycemia and glucose intolerance in the short period of 1 week. Moreover, plasma insulin levels were increased, likely due to compensatory β cell proliferation and β cell mass expansion triggered by expression changes of cell-cycle regulators. As the inhibitory peptide did not directly act on β cells per se, further genome-wide expression profiling of metabolically active tissues (liver, fat, muscle, and β cells) was used to identify potential mediators of this response. This pointed to Betatrophin, a secreted protein of 198 amino acids that is highly conserved in all mammalian species. Betatrophin shows increased expression in liver and fat in mouse models that expand β cell mass upon insulin resistance, pregnancy, or leptin deficiency. Intriguingly, transgenic overexpression of Betatrophin in the liver induces a rapid, robust, and specific increase of β cell proliferation and improves glucose tolerance in young adult mice. Together, these results suggest that Betatrophin may be one of the factors that we have searched for for over a decade, a hormone that triggers

compensatory β cell proliferation upon insulin resistance.

Although these are exciting findings, it is now important to understand how Betatrophin acts at the systemic, cellular, and molecular levels. Notably, genome-wide association studies have linked the human homolog gene *C19ORF80* to blood lipid levels (Teslovich et al., 2010). This association is functionally relevant, as three groups independently identified Betatrophin (formerly named Lipasin, RIFL, and ANGPTL8) as a nutritionally regulated factor that controls fatty acid metabolism and serum triglyceride levels (reviewed in Zhang and Abou-Samra, 2013). Thus, it will now be crucial to investigate whether Betatrophin alone or in combination with changes in lipid metabolism triggers β cell proliferation. Testing recombinant Betatrophin on isolated islets of Langerhans could clarify if the hormone acts directly on β cells. Furthermore, injections of biologically active Betatrophin in mice will reveal its dose response and specific and combinatorial effects on glucose and lipid metabolism. Finally, it will be important to determine (1) if Betatrophin on its own is necessary and (2) the key to trigger the compensatory β cell expansion upon insulin resistance using a Betatrophin mouse knockout model.

Once the direct effect of Betatrophin on β cell proliferation is clarified, the door to investigate the cellular and molecular mechanism of action is opened. The magnitude, rapidity, and specificity of β cell replication upon transgenic Betatrophin expression is remarkable, especially because it exceeds any compensatory proliferative response described so far in other mouse models (Yi et al., 2013). How Betatrophin elicits this potent response is currently unclear. One possibility is that Betatrophin might stimulate a specific subpopulation of β cells that is replication competent (Kushner, 2013) (Figure 1A), such as the rare insulin$^+$ self-renewing and multipotent progenitor population that was recently described in mouse and human islets (Smukler et al., 2011). Another possibility is that Betatrophin acts on β cells alone or in combination with other secreted factors in a synergistic or additive manner. For example, the combination of lipids and pregnancy hormones has been shown to additively regulate β cell proliferation during gestation (Brelje et al., 2008). The identification of receptors and signaling pathways that regulate β cell proliferation upon Betatrophin gain- and loss-of-function will address these issues. Insulin receptor signaling may not mediate this response since Betatrophin was discovered in a pharmacological model of insulin resistance. However, studying G protein-coupled, ion channel- linked, or enzyme-linked receptors and downstream pathway activation could provide insights into how the hormone regulates cell-cycle activators and inhibitors that tightly balance β cell proliferation (Figure 1B). Clarifying Betatrophin's mechanism of action and generating biological active hormone will move regenerative therapy one step closer to the clinic.

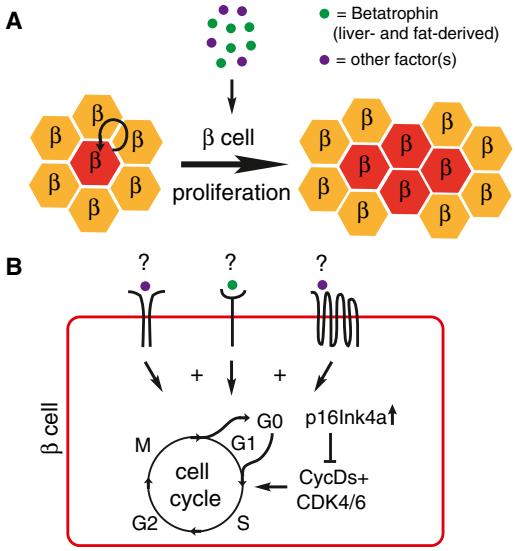

Figure 1. β Cell Proliferation Is Induced by Betatrophin by an as-of-yet Unknown Mechanism

(A) The Betatrophin hormone is upregulated in liver and white and brown fat during compensatory β cell proliferation. It either acts alone or in combination with other factor(s) to increase β cell proliferation and mass. The islet of Langerhans contains replication-refractory (orange) and replication-competent β cells (red) that might differentially react to mitogenic stimulation.

(B) Betatrophin and/or other circulating factors trigger a specific or combinatorial response via unknown receptors and signaling pathways. This leads to cell-cycle reentry of β cells through the regulation of cell-cycle activators and inhibitors.

Toward this aim, it will be necessary to show that Betatrophin acts selectively on β cells and does not trigger growth of other cell types in the mammalian body. Both beneficial regenerative effects on β cell replication and possible adverse effects due to changes in lipid metabolism have to be considered. Moreover, adaptive β cell regeneration severely declines with age in mammals (Kushner, 2013), and it is currently not clear whether promoting β cell replication or restoring β cell differentiation allows regenerative therapy (Talchai et al., 2012). Thus, it remains to be tested if Betatrophin can also elicit β cell mass expansion in aged or diabetic mice with restricted regenerative capacity or dedifferentiated β cells, respectively. Further experiments will soon tell us if Betatrophin allows regenerative therapy in humans.

REFERENCES

Bonner-Weir, S., and Weir, G.C. (2005). Nat. Biotechnol. *23*, 857–861.

Brelje, T.C., Bhagroo, N.V., Stout, L.E., and Sorenson, R.L. (2008). J. Endocrinol. *197*, 265–276.

El Ouaamari, A., Kawamori, D., Dirice, E., Liew, C.W., Shadrach, J.L., Hu, J., Katsuta, H., Hollister-Lock, J., Qian, W.J., Wagers, A.J., and Kulkarni, R.N. (2013). Cell Rep *3*, 401–410.

Kushner, J.A. (2013). J. Clin. Invest. *123*, 990–995.

Michael, M.D., Kulkarni, R.N., Postic, C., Previs, S.F., Shulman, G.I., Magnuson, M.A., and Kahn, C.R. (2000). Mol. Cell *6*, 87–97.

Smukler, S.R., Arntfield, M.E., Razavi, R., Bikopoulos, G., Karpowicz, P., Seaberg, R., Dai, F., Lee, S., Ahrens, R., Fraser, P.E., et al. (2011). Cell Stem Cell *8*, 281–293.

Talchai, C., Xuan, S., Lin, H.V., Sussel, L., and Accili, D. (2012). Cell *150*, 1223–1234.

Teslovich, T.M., Musunuru, K., Smith, A.V., Edmondson, A.C., Stylianou, I.M., Koseki, M., Pirruccello, J.P., Ripatti, S., Chasman, D.I., Willer, C.J., et al. (2010). Nature *466*, 707–713.

Yi, P., Park, J.S., and Melton, D.A. (2013). Cell *153*, 747–758.

Zhang, R., and Abou-Samra, A.B. (2013). Biochem. Biophys. Res. Commun. *432*, 401–405.